Electron. Physician

Electronic Physician
ISSN: 2008-5842

Original Article

ASSOCIATION OF LOW DENSITY LIPOPROTEIN LEVELS AND GLYCAEMIC CONTROL IN TYPE-2 DIABETES MELLITUS

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Bibliographic information of this paper for citing:
Yathish TR., Nachal Annamalai, and Vinutha shankar. Association of low density lipoprotein levels and glycaemic control in type-2 diabetes mellitus. Electron. Pysicician 2010, 2:24-32, Available at: http://www.ephysician.ir/2010/24-32.pdf

Received: 30 December 2009
Accepted: 10 January 2010
Published: 25 January 2010

Earlier diabetes mellitus (DM) was thought to be a disease of carbohydrate metabolism. Looking at the effects of insulin deficiency on carbohydrate and lipid metabolism, diabetes mellitus is now being called more a disease of lipid metabolism than carbohydrate metabolism. A cross-sectional study was conducted during March 2005 to March 2006 to study the low-density lipoproteins (LDL) levels in diabetes mellitus and its relation to glycaemic control. LDL levels were estimated. Comparison of lipid levels were made between group of diabetic patients with glycated hemoglobin less than 8.0% and a group of diabetic patients with glycated hemoglobin more than 8.0% and the controls. The lipid fractions i.e. total cholesterol (TC), triglycerides (TG), and low-density lipoprotein (LDL) levels were higher in the poorly controlled diabetes patients as compared to well controlled diabetic patients and nondiabetic patients. Increased levels of low-density lipoprotein may be a contributory factor to the high risk of atherosclerosis induced coronary artery disease observed in diabetes mellitus patients. Reduction of

Electronic Physician 2010; Vol 2, Pages 24-32

Keywords: low- density lipoprotein; glycosylated hemoglobin; type-2 diabetes mellitus

INTRODUCTION

Diabetes mellitus (D.M) is the commonest endocrine disease affecting mankind. The incidence of disease is on a rise not only in developed countries but also in developing countries. Diabetes mellitus is a metabolic disorder characterized by elevated fasting and postprandial blood glucose level and variety of multisystem complications, mainly in the blood vessels of eye, kidney, nervous system and integument. The heavy toll of death each year is due to its complications, which is usually common in age group 40-60 years affecting both sexes equally. The complications are more prevalent among the people of lower socioeconomic status because of negligence, illiteracy, poverty etc.

Coronary artery disease (CAD) especially Myocardial Infarction (MI) has reached enormous proportions striking more and more young subjects especially in patients with diabetes mellitus. It will result in greatest epidemic which mankind has ever faced in coming years unless we are able to reverse the trends by concentrated results into its cause and its prevention.

Among the very many risk factors identified for acceleration of the atherosclerotic process and thus predisposition to ischemic heart disease are hyperlipidemia and hyper lipoproteinemias. Cholesterol was incriminated as an etiologic factor for atherosclerosis long back when cholesterol was found in the atheromatus plaques. Various studies around the world have well established that low density lipoprotein, and very low density lipoprotein (VLDL) are atherogenic whereas high density lipoprotein (HDL) is a protective factor against coronary atherosclerosis and hence against MI.The present study was designed to estimate low-density lipoproteins (LDL) levels in diabetes mellitus and its relation to glycaemic control.

Aims and objectives of the study:
1. To study the levels of low-density lipoprotein cholesterol in type-2 diabetes mellitus.
2. To study the relation of low-density lipoprotein cholesterol to glycaemic control, as estimated by glycosylated hemoglobin concentration.

METHODS

The study group comprise of 50 subjects above 30 years of age having Type-2 diabetes mellitus. The control group comprise of 50 healthy subjects above 30 years of age. Cases are collected from outpatients and inpatients visiting R.L.Jalappa hospital and S.N.R. hospital attached to Sri Devraj Urs Medical College, Tamaka, Kolar, Karnataka, India and 50 age matched controls. History was taken in detail with informed consent and general physical examination was done after the clearance from ethical committee. Subjects with history of hypertension, lung or cardiac disease, smoking and alcoholism, on any drug affecting lipid levels of plasma are excluded from the study. Blood Samples are collected between 7 AM to 8 AM after overnight fasting. Lipid levels are estimated

by standard method. Low density lipoproteins are calculated by Friedewald's formula (1972):

Low Density Lipoprotein= Total Cholesterol- High Density Lipoprotein - Triglycerides /5

Glycosylated hemoglobin (HbA1c levels) was estimated by using Glycohemoglobin Reagent set, provided by Pointe Scientific Inc. Study group was again divided into two groups:

Group A. Poor glycemic control- HbA1c levels >8.0%

Group B. good glycemic control- HbA1c levels <8.0%

RESULTS

One hundred male subjects were selected as per the criteria laid down in the methods and materials sections for the present study .They were grouped as study group (Group A and Group B) and controls (Group C).Lipid levels and glycosylated hemoglobin levels were estimated in all groups. The data collected have been statistically analyzed and discussed. Lipid levels and glycosylated hemoglobin levels were compared between the three groups and the results discussed. The data was suitably arranged into suitable tables from the master chart for discussion under different headings. Analysis was performed using SPSS 8.0 statistical package for windows .Continuous variables are expressed as the mean + standard deviation and qualitative data as percentages. Comparison of patient's features was performed using Student's t test for unpaired data. Pearson correlation coefficient test (r value) was carried out to known the correlation of HbA1C and LDL.Chi-sqaure test was carried out to evaluate the significance of CAD in different groups. The mean difference is significant at $P<0.05$ level. Conclusion was drawn based on outcome of this statistical treatment.

Table 1 shows the distribution of the subjects according to the age. The youngest subject in the study group is aged 32 years and the oldest aged 68 years. The youngest subject in the control group is aged 31 years and the oldest aged 69 years. The mean age of the study group was 48.56 years and control group was 48.96 years. The maximum incidence of the coronary artery disease was found in the age group of 40-50 years.

Study group is further subdivided into

1. Poorly controlled DM (Group A):HbA1C >8%
2. Well controlled DM (Group B): HbA1C <8%

Table1: Distribution of subjects depending on age

Age group (Years)	Study group	Control group
30-39	8	**10**
40-49	21	**20**
50-59	12	**10**
>60	9	**10**
Total	**50**	**50**

Table 2 shows distribution of study group depending on age. The youngest subject in the Group A is aged 32 years and the oldest aged 64 years. The youngest subject in the Group B is aged 35 years and the oldest aged 68 years. The mean age of the Group A was 48.32 years and Group B was 48.80 years.

Table2: Distribution of study group depending on age

Age group (Years)	Poorly controlled DM	Well controlled DM
30-39	5	3
40-49	10	11
50-59	5	7
>60	5	4
Total	25	25

Table 3 shows HbA1C levels and LDL levels in different groups. HbA1C is significantly higher in the poorly controlled diabetes mellitus patients. It shows that as the glycaemic level increases, the LDL level also increases.LDL levels are significantly higher in poorly controlled diabetes patients whose HbA1C levels were elevated. There is a high correlation between HbA1C and LDL levels (Pearson correlation coefficient) in all the three groups ($P<0.01$).

Table 4 shows the mean values and standard deviations of the various lipid fractions in Group-A (poorly controlled diabetics) in comparison to that of Group-B (Well controlled diabetics) and Group C (Control) as well as the similar comparison between Groups B and C. It can be seen that mean value of all lipid fractions TC, HDL-C, LDL, TC/HDL, LDL/HDL are higher in the poorly controlled diabetics when compared to Group-B and is statistically significant. The TG was higher in Group-B than in poorly-controlled diabetics but is not statistically significant. It can also be seen that mean value of all lipid fractions TC, TG, LDL, TC/HDL, LDL/HDL are higher in the poorly controlled diabetics when compared to controls and is statistically significant. The HDL-Ch was higher in controls than in poorly controlled diabetics and is a safety factor. According to Table 3, the mean value of Triglycerides and TC/HDL are higher in the well controlled diabetics when compared to controls and is statistically significant. The TC, LDL-Ch and LDL/HDL did not show much change and is not statistically significant. The HDL-Ch was higher in controls than in well-controlled diabetics and is a safety factor.

Table3: HbA_{1C} and LDL levels in different groups

Subjects	HbA_{1C} LEVELS	LDL LEVELS	SIGNIFICANCE
Group A	9.61 $\pm$ 1.58	156 $\pm$ 25.09	r =+0.9966, P<0.0001
Group B	5.61 $\pm$ 1.33	91.28 $\pm$ 21.59	r =+0.9999, P<0.0001
Group C	5.62 $\pm$ 1.65	90.54 $\pm$ 28.77	r =+0.9709, P<0.01

TABLE 4: Comparison of lipid levels in different groups

Subjects		NO. of cases	TC	TG	HDL-C	LDL-C	TC/HDL	LDL/HDL
Group A		25	224.88 ± 29.75	179.40 ± 59.90	36.20 ± 6.14	156.00 ± 25.09	6.36 ± 1.47	4.23 ± 0.84
Group B		25	171.16 ± 17.58	213.04 ± 111.19	34.68 ± 4.83	91.28 ± 21.59	5.03 ± 0.91	2.65 ± 0.84
Group C		50	162.30 ± 33.67	147.44 ± 43.64	41.46 ± 8.18	90.54 ± 28.77	4.04 ± 1.03	2.33 ± 0.81
A-B	**t**	-	7.77	1.33	0.97	9.77	2.33	6.58
	P	-	<0.001	>0.05	>0.05	<0.001	<0.05	<0.001
	Sig.	-	VHSS[2]	NSS[3]	NSS	VHSS	SS[1]	VHSS
A-C	**t**	-	8.23	2.37	3.11	10.13	7.09	9.41
	P	-	<0.001	<0.05	<0.01	<0.001	<0.001	<0.001
	Sig.	-	VHSS	SS	HSS	VHSS	VHSS	VHSS
B-C	**t**	-	0.15	2.84	4.49	0.13	4.25	1.58
	P	-	>0.05	<0.01	<0.001	>0.05	<0.001	>0.05
	Sig.	-	NSS	HSS	VHSS	NSS	VHSS	NSS

1: Statistically Significant (SS)
2: Very Highly Statistically Significant (VHSS)
3: Not Statistically Significant (NSS)

DISCUSSION

Diabetes mellitus acts as a major risk factor for atherosclerosis either alone or in combination with other major risk factors such as diet, smoking, body weight etc.It has been found that patients with type-2 diabetes mellitus suffer from dyslipidemia which in turn leads to various vascular complications. In this study, patients with type-2 diabetes mellitus were grouped as poorly controlled and well controlled groups depending on their glycosylated hemoglobin levels and their lipid levels are compared with that of normal subjects. The results are analyzed and discussed below.

The present study has shown that the lipid fraction, TC, TG, LDL, VLDL, TC/HDL and LDL/HDL ratios are higher in DM

group than healthy controls as seen in the tables 4, 5 and 6 which are in accordance with most of the previous reports by various workers. In the present study except TG and VLDL, all other changes are statistically significant (P<0.01). The HDL was also low in DM group and was statistically significant (P<0.01). This goes in favor of many other studies. Formation of glycated hemoglobin is essentially irreversible, and the blood levels depend on both the life span of the red blood cell (average 120 days) and the blood glucose concentration. Because the rate of formation of glycated hemoglobin is directly proportional to the concentration of glucose in the blood .The glycated hemoglobin concentration represents the integrated values for glucose over the preceding 6 to 8 weeks. This provides an additional criterion for assessing glucose controls because glycated hemoglobin values are free from day to day glucose fluctuations and are unaffected by exercise or recent food ingestion(1). The glycated hemoglobin (HbA1C) test measures the percentage of that glycated hemoglobin, offering a snapshot of the average blood sugar control for the past few months.

Relationship between IDL and glycaemic control:

The mean and standard deviation of HbA1C in the three groups, GroupA, Group B, and Group C are 9.61+1.58, 5.61+1.33 and 5.62+1.65 respectively and the mean and standard deviation of LDL levels in the three groups, GroupA, Group B, and Group C are 156+25.09, 91.28+21.59 and 90.54+28.77 respectively.LDL levels are significantly higher in the poorly controlled diabetes patients whose glycosylated hemoglobin levels are elevated. There is a high correlation between the HbA1C levels and LDL levels in the poorly controlled group (R =0.997, P<0.01).

The finding of the present study is in conformity with the earlier studies done by Ramirez LC, Pacheco CA, Lackner C, et al.and Wagner Am, Jorba O, Rigla M et al. Wagner Am, Jorba O, Rigla M et al studied the effect of improving glycemic control on low-density lipoprotein particle size in 33 type-2 diabetes mellitus patients in a longitudinal intervention study. It was found that with glycaemia control a significant reduction in the LDL- cholesterol and ApoB and an increase in HDL- cholesterol and Apo AI were seen (2). Ramirez LC, Pacheco CA, Lackner C, et al. studied 60 diabetic patients with HbA1c with levels of 8.0% or higher had higher (25mg/dl) median levels of lipoprotein (a) when compared with either 93 normal controls (8.8 mg/dl) Or 33 diabetic patients with less than 8.0% (7.5mg/dl) (p=0.008 and p=0.012 respectively). He concluded that Lipoprotein (a) levels are elevated in poorly controlled diabetic patients (3).

The prevalence of dyslipidaemia in children with insulin dependent diabetes mellitus (IDDM) and its relation to glycaemic control was studied in a group of 51 diabetic children and a control population of 132 schoolchildren. Serum total cholesterol, triglycerides, and apolipoprotein (apo) B concentrations increased with worsening control, while serum high density lipoprotein cholesterol and apoA-I concentrations were unaltered (4).

Another study showed Triglycerides, LDL-cholesterol, and total serum lipids levels of poorly diabetic children (HbA1c > 8 %), were respectively higher (p<0.01), (p<0.05) and (p<0.01) than those of the control group. However, HDL-cholesterol level was significantly lower (p<0.01) in poorly diabetic children than in control group. They concluded increased levels of LDL cholesterol and triglycerides levels showed

that especially poorly controlled diabetes mellitus children present a high risk of atherosclerosis and vascular complications of diabetes mellitus. They showed a significant relationship between the lipid profile and the poor glycaemic control in diabetic children (5).

Glycosylation of low density lipoproteins obtained from 16 patients with Type 1 (insulin-dependent) diabetes and from 16 age-, sex-, and race-matched controls, was determined. Glycosylation of low density lipoproteins in the diabetic patients was significantly higher ($p < 0.001$) than in the control subjects, and was significantly correlated with haemoglobin A1c, ($p < 0.01$), glycosylation of plasma proteins, ($p < 0.001$), and mean home blood glucose, ($p < 0.01$). This study confirms that, in diabetic patients, increased glycosylation of low density lipoprotein occurs to an extent which correlates closely with other commonly used indices of glycaemic control(6).

Another study showed hyperglycaemia has a potent but reversible effect on LDL oxidation and that age may independently enhance LDL susceptibility to oxidation. These pathophysiological effects may play an important role in determining vascular complications and atherogenesis in poorly controlled type 1 diabetic patients (7). Another study concluded that both glycaemic control and familial factors may be important determinants of lipid levels in young people with diabetes. Both may contribute to the subsequent risk of cardiovascular disease and possibly the development of incipient diabetic nephropathy (8).

In this study, they evaluated whether the level of glycemic control affected the oxidizability of LDL in patients with type2 diabetes mellitus (DM). In incubation with 40.MU.M FeSO4, the thiobarbituric acid-reactive substances (TBARS) level in type2 DM patients was significantly higher than that of non-DM subjects. TBARS levels of the poorly-controlled group were significantly higher than those of the well-controlled group when incubated with 10 and 40.MU.M FeSO4. The lipid profile and .ALPHA.-tocopherol content of LDL did not differ significantly in each group. These results suggest that sustained hyperglycemia leads to LDL glycation and contributes to acceleration of LDL oxidation (9).

Many others studied the effect of insulin and sulfonylurea therapy on low density lipoprotein subfractions, effect of obesity, distribution of low density lipoprotein (10-16). Wei M, Gaskill SP, Haffner SM, Stern MP studied the effects of diabetes and level of glycaemia on all-cause and cardiovascular mortality (17). The basis of this finding is whenever the glycaemic level increases as in the diabetes mellitus patients; the LDL will get glycated.This chemically modified glycated LDL causes inhibition of the ability of LDL to interact with the LDL receptors. This in turn inhibits the ability of the LDL to be metabolized by the LDL receptor pathway. Thus plasma LDL levels are high and atherosclerosis occurs early in life (18).

Another mechanism shows chronic hyperglycemia leads to nonenzymatic glycation of LDL and collagen fibers leading to formation of Schiff base which in turn forms amadori products. This causes tissue damage by reactivity and protein cross linking. The glycated LDL also binds with glycated collagen leading to heavy cholesterol deposition which is the first step in the pathogenesis of atherosclerosis leading to coronary artery disease (19).

CONCLUSION

In summary, the findings from our study suggest that:

1. Low density lipoprotein levels are elevated in poorly controlled diabetes patients. Increased levels of Low-density lipoprotein may be a contributory factor to the high risk of atherosclerosis observed in diabetes patients.
2. Glycaemic optimization is a good tool to improve the components of diabetes dyslipidemia. Among the different lipids, the elevation of Low-density lipoprotein was contributing more for the development of coronary artery disease.
4. Reduction of glycosylated hemoglobin is likely to reduce the risk of complication mainly coronary artery disease, with the lowest risk being in those with glycosylated hemoglobin values in the normal range i.e. less than 8.0%
5. However probably not only glycaemic optimization but also lifestyle Intervention plays a role in the improvement of the different components of diabetes dyslipidemia.
6. Diet also has a positive correlation with myocardial infraction as patients following a mixed diet had significantly higher serum cholesterol and Low Density Lipoprotein levels than those following a vegetarian diet.

ACKNOWLEDGEMENT:

My sincere thanks to Principal of Sri Devaraj Urs medical university for permitting me to prepare this paper and Faculty members of department of physiology for their kind cooperation and encouragement.

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